## REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

### I. Status of the Claims

Upon entry of the amendments, claims 1 and 44-99 will remain pending in the application. Claims 1, 44-55, 63-76 and 84-85 are under examination, while claims 56-62, 77-83 and 86-99 are withdrawn from consideration. Claims 1 and 64 presently are being amended. No claims presently are being added or canceled.

### II. Sequence Requirements

The Office objected to the specification because Tables III and IV allegedly fail to comply with the sequence requirements of 37 C.F.R. §§ 1.821-1.825.

The foregoing amendments to those tables fully address the objection. Accordingly, Applicants request withdrawal of the objection.

### III. The Claims are Enabled

Claims 64-76 and 84-85 were rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly "does not reasonably provide enablement for having a vaccine composition comprising [an] antigen complex that is able to protect [against] HCV infection." The examiner acknowledged that the specification is "enabling for an immunogenic composition comprising HCV full length core antigen (1-191) adsorbed onto the case-like structure of ISCOMATRIX by ionic interaction, wherein said Core-ISCOM immune complex is able to produce a strong cytotoxic T lymphocyte (CTL) immune response against a specific core antigen epitope." According to the examiner, however, the strong immune response is not predictive of "a sustained immunity that is able to prevent HCV infection." Applicants traverse the rejection.

The rejection is inapplicable to the amended claims, which simply refer to "a composition comprising an immunogenic complex," and not a vaccine. Because the specification enables one skilled in the art to produce compositions that induce a strong and specific CTL immune response (a fact already acknowledged by the examiner), the full scope

of claims 64-76 and 84-85 is enabled. Accordingly, Applicants request withdrawal of the enablement rejection.

## IV. The Claimed Invention is Novel

Claims 1, 46-55, 63-64, 66-76 and 85 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 98/15287A1 ("Garcon I") and were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by WO 99/11241A1 ("Garcon II"). Applicants traverse the rejections.

All of the rejected claims require "an immunogenic complex comprising a negatively charged organic complex and a charged antigen, which organic complex and antigen are electrostatically associated," but Garcon neither teaches nor suggests such an immunogenic complex. Rather, the adjuvant compositions disclosed in Garcon I have aluminum salts as an essential integer. According to the teachings of Garcon I, antigen was first adsorbed to alum before the addition of MPL or QS21. *See, e.g.*, page 7, lines 15-24 and page 14, lines 8-12 of Garcon I. Thus, antigen was adsorbed to an *inorganic* carrier before an *organic* carrier was even introduced, indicating that there was no direct electrostatic interaction between the organic carrier and antigen. Additionally, neither the MPL nor the QS21 taught by Garcon I is an organic complex. Thus, Garcon I lacks any teaching whatsoever of a negatively charged organic complex in electrostatic association with a charged antigen.

All of the rejected claims also exclude compositions in which the immunogenic complex is an oil-in-water emulsion. That, however, is the type of adjuvant formulation described by Garcon II.

For at least these reasons, the cited art does not anticipate the rejected claims. Accordingly, Applicants request withdrawal of the anticipation rejections.

## V. The Claimed Invention is Non-Obvious

Claims 1, 44-55, 63-76 and 84-85 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Garcon I and Cooper *et al., Immunity*, 10: 439-449(1999) ("Cooper") and John *et al., Hepatology*, 30(4): 1037-1044 (1999) ("John"). In particular, the rejection asserted that "it would have been obvious for an artisan with ordinary skill in the art to be

motivated by the disclosures of WO 98/15287A1, Cooper et al. and John et al. to make an immunogenic composition mainly by using the antigen epitopes from the core antigen taught by Cooper and John plus an adjuvant disclosed by WO 98/15287A1, because John et al. teach that the HCV Core antigen is more reliable for inducing a T cell mediated immune response among different isolates against HCV infection since it has less mutation among different isolates of HCV, and the addition of adjuvant disclosed by WO 98/15287A1 will remedy the week [sic] immune response of Core antigen disclosed by John and Cooper." Applicants traverse the rejection.

Again, the compositions of Garcon I require alum. According to the teachings of Garcon I, antigen was first adsorbed to alum before the addition of MPL or QS21. *See, e.g.*, page 7, lines 15-24 and page 14, lines 8-12 of Garcon I. Thus, antigen was adsorbed to an *inorganic* carrier before an *organic* carrier was even introduced, indicating that there was no direct electrostatic interaction between the organic carrier and antigen. Additionally, neither the MPL nor the QS21 taught by Garcon I is an organic complex. Thus, Garcon I lacks any teaching whatsoever of a negatively charged organic complex in electrostatic association with a charged antigen. Moreover, there is no disclosure or teaching in Garcon I that would motivate a skilled artisan to make an immunogenic complex in which a negatively charged organic complex and a charged antigen are electrostatically associated. Garcon also lacks any evidence for the induction of CTLs, and only shows evidence of Th1 responses. Finally, although Garcon I disclosed HCV antigen, that disclosure was part of a catch-all provision for infectious agents and the specification provides no disclosure of individual HCV antigens, nor how to choose which antigen(s) would be included in an immunogenic complex, nor how to optimize a CTL response to antigen(s).

Cooper et al. examined CTL responses in HCV-infected chimps, particularly in those that had cleared an HCV infection. Despite the rejection's assertion that Cooper teaches a method for identifying HCV immunogenic epitopes "that are able to induce a strong CTL immune response against HCV antigen," Cooper does not disclose an immunogenic composition, but merely suggests that certain HCV antigens might be important in vaccines, based on an examination of which HCV antigens induced CTL responses in 'cured' chimps. Chimpanzees, however, may not respond to HCV in the same manner as humans.

Accordingly, a demonstration that CTLs in chimps react with specific epitopes is not a teaching or suggestion that the same epitopes are relevant in humans.

John et al. reports a study that analyzed nucleotide changes in core and envelope products over time in HCV-infected patients. Although the rejection stated that John teaches that the HCV core antigen is more reliable for inducing a T-cell mediated response against HCV infection, John actually lacks any disclosure or teaching of immunogenic complexes or of inducing a CTL response. In particular, John lacks any disclosure or teaching that would lead a skilled artisan to use the core or envelope antigens in an immunogenic complex as claimed in the present claims.

Based on the work of Cooper, it was known that CTL responses were required for viral clearance, but it was not known what HCV antigens should be used or how they should be formulated to induce strong and persistent CTL responses. The presently claimed invention provides, for the first time, a formulation that is able to achieve such responses to a range of HCV antigens, without the need to identify CTL epitopes within those antigens, specifically by presenting the antigens in the form of an immunogenic complex in which a negatively charged organic complex which comprises a saponin and a sterol is electrostatically associated with a charged antigen which comprises one or more HCV polypeptides. The combination of prior art references relied on the rejection does not teach or suggest such an immunogenic complex. Accordingly, Applicants request withdrawal of the rejection.

## VI. Concluding Remarks

Applicants believe that this application is now in condition for allowance, and request favorable reconsideration of it.

If the Examiner believes and any issues remain unresolved or that an interview would help to advance prosecution of the application, he or she is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

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